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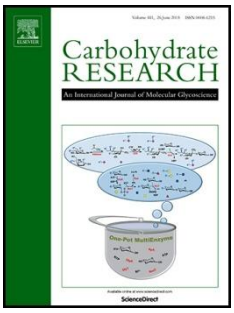

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Sugar-based Novel Chiral Macrocycles for Inclusion Applications and Chiral Recognition

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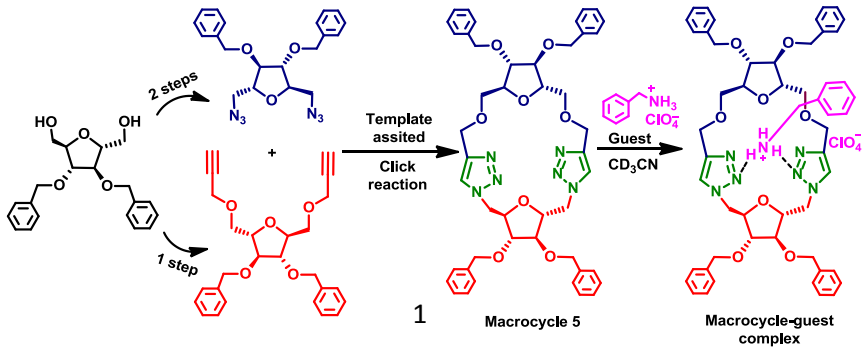
Highlights

1. A convergent template assisted synthesis of sugar-based chiral macrocycles has been described.
2. The host-guest inclusion studies have revealed selective significant interactions of the synthesized macrocycle with the primary ammonium salt compared to the secondary salt.
3. The synthesized chiral macrocyle also discriminates between D- and L-phenylalanine methyl ester hydrochlorides as revealed by ^{1}H NMR spectral studies on the mixture of the host and the guest molecules.

Graphical Abstract

A highly convergent template assisted synthesis of chiral macrocycles, which are cyclic homodimer of azido-alkyne furanose sugar derivatives, has been successfully achieved and evaluated for host-guest inclusion complex formation ability using benzyl- and dibenzyl ammonium perchlorate salt as guests. One of the chiral macrocyles showed recognition for D- and L-phenylalanine methyl ester hydrochloride salts.



A convergent template assisted synthesis of sugar-based chiral macrocycles has been achieved. The host-guest inclusion studies have revealed significant interactions of the synthesized macrocycle with primary over secondary ammonium salt. The chiral macrocyle also discriminates between D- and L-phenylalanine methyl ester hydrochlorides as revealed by ^{1}H NMR spectral studies on the mixture of the host and the guest molecules.

Keywords: Macrocycle, Click reaction, Template assisted, Benzyl ammonium perchlorate, Phenylalanine, Chiral recognition.

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1. Introduction

Sugar-based macrocycles are of immense importance owing to their ease of accessibility from natural resources, multifunctional nature, presence of geometrical constraints and also due to the chiral nature of the sugar which provides key specificities in molecular recognition processes.[1,2] Like naturally occurring sugar-based macrocycles, their synthetic counterparts are also interesting because of their complex structure and synthetic challenges. They have diverse applications as supramolecular architectures,[3] medicines,[4] biomimetic receptors,[5] molecular pores,[6] chiral recognition agents,[7] *etc.*

Recently, some sugar-based macrocycles with triazole linkage have been synthesized involving copper catalyzed alkyne-azide cycloaddition reaction (CuAAC).[8-14] These types of macrocycles find great applications as inclusion hosts and as pharmacophores.[15] In course of C_n-symmetric synthesis, cyclodimerization / cyclooligomerization of azido-alkyne sugars or synthesis of carbohydrate-peptide

hybrids have been reported using glucopyranosides and furanosides.[8,9,16,17] The synthesis of C_n-symmetric macrocycles is a challenging task often due to insufficient product yield and to overcome the problem different approaches utilizing π-π stacking, π-donor / π-acceptor interactions, hydrogen bonding of non-metallic templates like simple aromatic compounds has been tried.[4,9,11,16,18-21]

In the present work, we have designed and developed a simple and facile template assisted synthesis of chiral sugar-based macrocycles which are homodimer of azido-alkyne sugars derived from 2,5-anhydro-D-mannitol (Fig. 1). Interestingly, one of the synthesized macrocycles exhibited appreciable interaction with the primary ammonium salt, *i.e.* benzyl ammonium perchlorate over dibenzyl ammonium perchlorate salts and also showed chiral discrimination between L- and D-phenylalanine methyl ester hydrochlorides.

2. Result and Discussion

2.1 Synthesis

The synthesis of chiral sugar-based macrocycles **5** and **7** has been illustrated in Schemes 1 and 2. The 2,5-anhydro-D-mannitol (**1**) was synthesized from commercially available D-glucosamine hydrochloride in 80 % overall yields in three steps, which was again converted to the partially benzylated furanoside, *i.e.* 3,4-di-*O*-benzyl-2,5-anhydro-D-mannitol (**2)** *via* its perbenzylation, partial acetolysis followed by deacetylation using NaOMe-methanol in 70 % overall yields following literature procedure**.**[22] In a parallel set of reactions compound **2** was converted to 3,4-di-*O*-benzyl-1,6-di-*O*-propargyl-2,5-anhydro-D-mannitol (**3**) using propargyl bromide and *N-tetra*-butyl ammonium hydrogen sulphate as phase transfer catalyst in 75 % yields

and to 1,6-diazido-3,4-di-*O*-benzyl-2,5-anhydro-D-mannitol (**4**) by mesylation using MsCl-pyridine followed by azidation with NaN_3 in DMF in 77 % yields (Scheme 1).

The synthesis of macrocycle **5** was attempted through cycloaddition reaction between sugar alkyne **3** and azide **4** using conventional click condition,[23] *i.e.* in the presence of $CuSO_4.5H_2O$ and sodium ascorbate in *t*-butanol-water-THF (1:1:2; 1 mL / 100 mg of equimolar mixture of compounds **3** and **4**). The reaction led to the formation of a complex mixture and even after repeated column-chromatography the desired macrocycle **5** was obtained only in 6 % yield in 28 h (entry 1, Table 1). To improve the yield, the click reaction was performed under same condition in the presence of ethylene diamine dihydrochloride as template to assist the macrocyclization, but it does not led to any improvement in the efficiency of the reaction (entry 2, Table 1). The use of *S*-phenyl ethyl ammonium acetate as template instead of ethylene diamine dihydrochloride in macrocyclization reaction resulted in three fold improvement in the yield of compound **5** along with the decrease in the reaction time (entry 3, Table 1). The improvement in yield of macrocycle formation could be due to the pre-organization of the azide and the alkyne substrates by virtue of the interaction of ammonium ion of the template with different hydrogen bond acceptor sites of both the sugar units **3** and **4** as well as with the resulted triazole ring of the macrocycle **5**. In addition, the interaction of phenyl group of the template with the benzyl groups of two sugar moieties *via* π-π stacking may also helps in holding the two reacting sugar units in closer proximity. The yield of macrocyclization affording compound **5** was further improved by six fold with respect to entry 1 and almost 1.7 fold with respect to entry 3 in Table 1 by carrying out the reaction at 20 times higher dilution of *t*-butanol-water-

THF (1:1:2 ratio), *i.e.* at 20 mL solvent / 100 mg of equimolar mixture of compounds **3** and **4** (entry 4, Table 1). The enhancement in yield at higher dilution may be attributed to the enhancement of the opportunity for intramolecular azide-alkyne coupling over intermolecular coupling.[24] Thus in a typical reaction an equimolar mixture of sugar alkyne **3** and azide **4**, $CuSO_4.5H_2O$, sodium ascorbate, *S*-phenyl ethyl ammonium acetate salt and *t*-butanol-water-THF (1:1:2) was stirred at 30 ^oC for 6 h. On completion, the reaction mixture was dried under reduced pressure and the product was extracted with chloroform. The residue obtained by removal of solvent was purified by silica gel column chromatography to afford the pure macrocycle **5** as off-white solid in 30 % yield. The use of *R*-phenyl ethyl ammonium acetate salt instead of its *S*-enantiomer as a template in the macrocyclization reaction proved to be less efficient as there was minor dip in the yield of the reaction (entry 5, Table 1).

The methodology developed for the synthesis of macrocycle **5** was further used for the synthesis of a novel sugar-based chiral macrocycle **7** having phenyl linker between two *bis*-triazolyl-sugar units. Thus, the coupling of azido sugar **4** with *bis*-triazolyl-sugar unit **6** under optimized condition (as in entry 4, Table 1) afforded macrocycle **7** as yellowish solid in 28 % yield. The *bis*-triazolyl-sugar unit **6**, in turn was obtained from dialkyne sugar **3** in two steps, *i.e.* by its coupling with 4-trimethylsilylethynylphenyl azide in the presence of $CuSO_4.5H_2O$, sodium ascorbate followed by desilylation of the alkyne moiety of the coupled product with TBAF in DMF at 30 ^oC in 77 % overall yields (Scheme 2).[25] The aim for the incorporation of phenyl linkers in the homodimer macrocycle **7** was to enhance the electron density in the ring by placing a π donor linker in the cavity.

The structure of the synthesized macrocycle **5** and the intermediates **1**, **2**, **3**, **4** and **6** were confirmed by its IR, ^{1}H-, ^{13}C NMR, HSQC, DEPT-135 and HRMS spectral data analysis. The structure of the macrocycle **7** was confirmed by its UV, IR, ^{1}H NMR and HRMS spectral data analysis. The ^{13}C NMR spectrum and further studies on macrocycle **7** could not be taken up due to its highly insoluble nature in any of the deuterated solvents or in TFA.

The structures of known compounds **1** and **2** were further confirmed by comparison of their physical and spectral (IR, ^{1}H, ^{13}C NMR, and HRMS) data with those reported in the literature.[22] Compound **5** was found to be chiral and has shown specific rotation, $[\alpha]_D^{30} = +40$ (*c* 0.1 $CHCl_3$).

2.2. ^{1}H NMR Interaction Studies

The synthesis of sugar-based macrocycles **5** and **7** assisted by *S*-phenyl ethyl ammonium salt as template indicated about the possible interactions of ammonium ion with the electron rich core (hydrogen bond acceptor) of the compounds. This observation prompted us to perform host-guest inclusion studies on the synthesized macrocycle **5** with ammonium salts, such as benzyl- or dibenzyl ammonium perchlorate salts. The comparison of ^{1}H NMR spectrum of equimolar mixture of the macrocycle **5** and the benzyl ammonium perchlorate salt with the individual ^{1}H NMR spectrum of the macrocycle **5** and that of the salt in CD_3CN has revealed noteworthy interactions (Fig. 2).

The three protons of the NH_3^+ group of the guest salt appearing at δ 6.67 showed a downfield shift and appeared at δ 6.82 (Δ δ 0.15 ppm) together with the slight

broadening of this peak in the ^{1}H NMR spectrum of the host-guest complex. The broadening in peaks of the NH_3^+ group of guest salt in the ^{1}H NMR spectrum was attributed to the hydrogen bonding of its protons with nitrogen atom(s) of the triazole rings and with oxygen atom(s) present in the electron rich cavity of macrocycle **5**. This is complimented with the remarkably downfield shift of $\Delta\ \delta$ 0.16 ppm of the triazole ring protons, *i.e.* C-9H and C-10H appearing at δ 7.66 in the ^{1}H NMR spectrum of macrocycle **5** resonated at δ 7.82 in the host-guest complex. The downfield shift in protons of the triazole ring is due to the partial positive charge created in the ring by virtue of the hydrogen bond formation between the nitrogen atom(s) of the triazole rings with the protons of the NH_3^+ group of the guest salt. Furthermore, the CH_2 protons of the benzyl moiety of perchlorate salt appearing at δ 4.14 shows a slight upfield shift of $\Delta\ \delta$ 0.03 ppm in the ^{1}H NMR spectrum of the host-guest complex, because of the anisotropic effect of benzylic phenyl groups of macrocycle **5**. The spatial interactions of the CH_2 protons of the guest benzyl ammonium perchlorate salt with the benzylic CH_2 and other protons (C-1'H, C-6'H, C-7H, C-8H, C-2H, C-5H) of the macrocycle **5** was observed in the NOESY NMR spectrum of the host-guest complex (Fig. S12, SI), which explains that the guest molecule is in the close proximity with the host macrocycle. In addition, change in splitting patterns of other peaks has also been observed in the ^{1}H NMR spectrum of the host-guest assembly with respect to the individual ^{1}H NMR spectrum of the macrocycle **5** and the perchlorate salt.

The formation of host-guest inclusion complex was further ascertained by using HRMS spectrometry. The calculated value for the $[M\text{-}ClO_4]^+$ ion of the complex of macrocycle **5** and the guest ammonium salt is 922.4498 and the observed value was found to be 922.4479, which confirms the formation of host guest assembly (Fig. S15,

SI). Further, the association constant of the complex was calculated considering the downfield shift in the triazole ring protons of host macrocycle **5** present at δ 7.66 with respect to the chemical shift values of the same protons in the ^{1}H NMR spectrum of the host-guest complex taken at different molar ratios (Fig. 3). On the basis of the ^{1}H NMR titration experiments as above, the association constant K_a was found to be 45.9 M^{-1} (Fig. 4), which indicated the affinity of host macrocycle **5** towards hydrogen bond donor primary ammonium ion.

The possibility of formation of host-guest assembly between macrocycle **5** and secondary amine, dibenzyl ammonium perchlorate salt was studied using ^{1}H NMR spectroscopy. There was negligible change in the ^{1}H NMR spectrum recorded for the equimolar mixture of the macrocyclic host **5** and the secondary ammonium ion, and in the individual spectrum of two compounds (Fig. S16, SI). This reveals that the core of the macrocyclic host **5** is small enough to accommodate salts derived from primary amines only. In addition the centre of hydrogen bond donor is less in secondary amine than in primary amine, which will also lead to insufficient interaction between the host and the dibenzyl ammonium perchlorate salt.

The macrocyclic host **5** is chiral, which was confirmed by its specific rotation measurement. The chiral recognition capability of the cyclic host molecule was explored by recording ^{1}H NMR spectrum of equimolar mixture of host **5** and D / L phenylalanine methyl ester hydrochloride salt and by its comparison with the individual ^{1}H NMR spectrum of macrocycle **5** and D- & L- hydrochlorides in $CDCl_3$ (Fig. 5). The host-guest interaction of macrocycle **5** with L- phenylalanine methyl

ester hydrochloride salt was noteworthy. An upfield shift of Δ δ 0.12 ppm in the diastereotopic CH_2 protons of L-phenylalanine methyl ester hydrochloride appearing at δ 3.39 has been observed in the ^{1}H NMR spectrum of the host guest assembly, due to the anisotropic effect of phenyl rings present in host macrocycle **5**. The protons of triazole ring of macrocyclic host **5** appearing at δ 7.71 shifted downfield by Δ δ 0.18 ppm in the ^{1}H NMR spectrum of the host guest assembly. The change in the chemical shift position and the shape of peak of some other protons in the ^{1}H NMR spectrum of the host-guest assembly has also been observed with respect to the individual spectrum, but it cannot be distinguished because of the overlapping of peaks. Although, there was no appreciable change in the chemical shift values of protons of host-guest assembly of D- phenylalanine methyl ester hydrochloride and macrocycle **5**, as compared to their individual ^{1}H NMR spectrum, but the shape and the splitting pattern of diastereotopic protons of amino acid was clearly visible. This suggests that the macrocyclic host **5** interacts differently with D- / L- phenylalanine methyl ester hydrochloride or in other words it is able to discriminate between D- and L-amino acids (Fig. 5). Further, confirmation of the interactions between macrocycle **5** and L-phenylalanine methyl ester hydrochloride / D-phenylalanine methyl ester hydrochloride have been accomplished with the help of a geometrically optimized structures using hybrid Density Functional Theory (DFT). The energy minimized structure of macrocycle **5** and L-phenylalanine methyl ester hydrochloride complex supports hydrogen bonding and π-π interactions between host macrocycle and guest amino acid salt while macrocycle **5** and D-phenylalanine methyl ester hydrochloride complex does not support any such interactions, which clearly indicate the chiral discrimination of the two esters (Fig. 6 and 7).

3. Conclusion

In conclusion, we have successfully accomplished a highly efficient template assisted convergent synthesis of sugar-based chiral macrocycles **5** and **7**. To the best of our knowledge, it is the first example of utilization of two primary hydroxyl groups of the furanose sugar to provide adequate symmetry to the synthesized triazole linked macrocyclic compound. The discovery of *S*-phenyl ethyl ammonium perchlorate salt as template for macrocyclisation reaction led us to reveal the host-guest inclusion chemistry of the macrocyclic compound **5**. The inclusion chemistry of the host macrocycle is very specific and it recognizes benzyl ammonium perchlorate salt over dibenzyl ammonium perchlorate salt. This result prompted us to study the chiral recognition potential of the macrocyclic host **5**, which led to the finding that it discriminates between D- and L- phenylalanine methyl ester hydrochlorides very well. The synthesised macrocyclic system **5** could find potential applications as artificial receptor and as chiral recognition agent.

4. Experimental Section

4.1. General

Melting points were determined on Buchi M-560 instrument. The IR spectra were recorded on a Perkin-Elmer model 2000 FT-IR spectrometer by making KBr disc for solid samples and thin film for oils. The ^{1}H and ^{13}C NMR spectra were recorded at Jeol alpha-400 spectrometer at 400 and 100.6 MHz, respectively using TMS as internal standard. The chemical shift values are on δ scale and the coupling constants (J) are in Hz. The mass spectra recording have been done on a micro TOF-Q instrument from Bruker Daltonics, Bremen and 6520 Q-TOF instrument from Agilent Technologies on ESI positive mode. Optical rotations were measured on Rudolph Autopol II automatic polarimeter using light of 546 nm wavelength. Absorption spectra were recorded between 250 and 700 nm using

Pelkin-Elmer UV/Vis spectroscopy cell (1 cm). Analytical TLCs were performed on pre-coated Merck silica-gel $60F_{254}$ plates; the spots were detected either under UV light or by charring with 4 % alcoholic H_2SO_4. Silica gel (100-200 mesh) was used for column chromatography.

4.2. Synthesis of 3,4-di-*O*-benzyl-1,6-di-*O*-propargyl-2,5-anhydro-D-mannitol (**3**)

To a solution of compound **2** (200 mg, 0.58 mmol) in 20 mL toluene:20 % aq. NaOH (1:1) in a round bottom flask, tetrabutyl ammonium hydrogen sulphate (191 mg, 0.58 mmol) was added under stirring. Propargyl bromide (0.184 mL, 1.16 mmol) was added into the reaction mixture and the stirring continued at 30 ^oC for 3 h. The progress of reaction was monitored by TLC and after completion compound was extracted from the reaction mixture with ethyl acetate (3 x 50 mL). Combined organic layer was washed with saturated NaCl solution, dried over anhydrous Na_2SO_4 and then organic layer was concentrated at reduced pressure. The crude product thus obtained was purified by column chromatography over silica gel using ethyl acetate-petroleum ether as an eluent. Pure compound **3** was obtained as a white sticky solid in 75 % yield (183 mg). $[\alpha]_D^{27}$: +6.1 (*c* 0.1 $CHCl_3$); IR (cm^{-1}, film) 2866, 1085, 740; ^1H NMR (400 MHz, $CDCl_3$): 7.25-7.36 (m, 10H, 2 x *Ph*CH_2), 4.50-4.57 (m, 4H, 2 x PhC*H*$_2$), 4.16-4.17 (m, 6H, 2 x CH≡C-C*H*$_2$, C-2H, C-5H), 4.05 (d, 2H, *J* = 4.0 Hz, C-3H, C-4H), 3.63 (d, 4H, *J* = 5.6 Hz, C-1H and C-6H), 2.38 (t, 2H, *J* = 5.2 Hz, 2 x C*H*≡C); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 137.8 (C), 128.4 (CH), 127.8 (CH), 84.6 (CH), 81.4 (CH), 79.4 (C), 74.6 (CH), 71.9 (CH_2), 69.6 (CH_2), 58.5 (CH_2); HRMS (ESI) *m/z* calcd. for $C_{26}H_{29}O_5$ $[M+H]^+$ 421.2010, found 421.2011.

4.3. Synthesis of 1,6-diazido-3,4-di-*O*-benzyl-2,5-anhydro-D-mannitol (**4**)

Compound **2** (1 g, 2.906 mmol) dissolved in 10 mL pyridine, was cooled to -10 ^{o}C followed by dropwise addition of mesyl chloride (0.49 mL, 6.39 mmol). The reaction mixture was stirred at 30 ^{o}C for 4 h. The progress of the reaction was monitored by TLC. After completion, the compound from of reaction was extracted with ethyl acetate (3 x 100mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Dimesylated sugar obtained was purified by column chromatography over silica gel using chloroform- methanol as an eluent. The pure dimesylated sugar obtained was directly used for the next step. A mixture of dimesyl sugar (1 g, 2.13 mmol), sodium azide (0.35 g, 5.33 mmol) and DMF (15 mL) was stirred at 100 ^{o}C for 6 h in a round bottomed flask. The progress in the reaction was monitored with TLC. After completion, the reaction mixture was filtered and the mother liquor was evaporated. The crude residue was then purified by silica gel column chromatography using ethyl acetate-petroleum ether as the eluting solvents. Compound **4** was obtained as colourless oil in overall yields of 77 % (722 mg). $[\alpha]_D^{24}$: +71.5 (*c* 0.1 $CHCl_3$); IR (cm^{-1}, film): 2099, 1402 1084, 741; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.38 (m, 10H, 2 x *Ph*CH_2), 4.50-4.54 (m, 4H, 2 x PhC*H*$_2$), 4.19 (s, 2H, C-2H, C-5H), 4.01 (d, 2H, *J* = 4.4 Hz, C-3H, C-4H), 3.36 (d, 4H, *J* = 6.0 Hz, C-1H, C-6H); ^{13}C NMR (100.6MHz, $CDCl_3$): δ 137.2 (C), 128.5 (CH), 128.0 (CH), 127.7 (CH), 84.5 (CH), 81.5 (CH), 72.2 (CH_2), 52.0 (CH_2); HRMS (ESI) *m/z* calcd. for $C_{20}H_{23}N_6O_3$ $[M+H]^+$ 395.1826 , found 395.1826.

4.3. Synthesis of macrocyclic compound **5**

A mixture of compound **3** (200 mg, 0.47 mmol), compound **4** (187 mg, 0.47 mmol), $CuSO_4.5H_2O$ (48 mg, 0.194 mmol), sodium ascorbate (77 mg, 0.388 mmol) and *S*-phenyl ethyl ammonium acetate (57 mg, 0.47 mmol) in *t*-BuOH-water-THF (80 mL, 1:1:2 ratio) was stirred at 30 ^{o}C for 6 h. The progress of the reaction was monitored using TLC (3 % MeOH-$CHCl_3$). After completion, the reaction mixture was completely dried over reduced pressure by co-evaporating with toluene (3 x 2 mL). The residue thus obtained was dissolved in

chloroform, filtered and evaporated to dryness under reduced pressure. The residue was purified by column chromatography using silica gel as stationary phase and chloroform-methanol as the eluting solvents. Pure compound **5** was obtained as off-white solid in 30 % yield (122 mg). M.P.: 92-94 ^{o}C; $[\alpha]_D^{30}$: +40 (*c* 0.1 $CHCl_3$); IR (cm^{-1}, film): 2924, 1733, 1237, 777; ^{1}H NMR (400 MHz, CD_3CN): δ 7.66 (s, 2H, C-9H, 10H), 7.28-7.38 (m, 20H, 4 x *Ph*CH_2), 4.64 (s, 4H, 2 x PhC*H*$_2$), 4.42-4.56 (m, 14H, 2 x Ph*CH*$_2$, C-7H, C-8H, C-1'H, C-6'H, C-2H, C-5H), 4.07 (s, 2H, C-3H, C-4H), 3.99-4.01 (m, 2H, C-2'H, C-5'H), 3.87-3.88 (m, 2H, C-3'H, C-4'H), 3.55-3.64 (m, 4H, C-1H, C-6H); ^{13}C NMR (100.6MHz, CD_3CN): δ 146.9 (C), 139.2 (C), 138.8 (C), 129.4 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 124.7 (CH), 86.0 (CH), 85.2 (CH), 82.8 (CH), 82.0 (CH), 72.9 (CH_2), 72.6 (CH_2), 71.6 (CH_2), 64.9 (CH_2), 53.01 (CH_2); HRMS (ESI) *m/z* calcd for $C_{46}H_{51}N_6O_8$ $[M+H]^+$ 815.3763 , found 815.3764.

4.4. Synthesis of *bis*-triazolyl-sugar (**6**)

A mixture of compound **3** (500 mg, 1.19 mmol), 4-azido phenyl TMS acetylene (520 mg, 2.38 mmol), CuI (4 mg, 0.21 mmol) in THF-ethanol-water (1:1:1, 6 mL) in a round bottom flask was stirred at 30 ^{o}C for 24 hrs. The progress of the reaction was monitored by TLC (1 % MeOH-$CHCl_3$). After completion of the reaction, solvent was removed under reduced pressure. The silylated sugar (250 mg, 0.29 mmol) was then dissolved in THF (25 mL), cooled to 0 ^{o}C followed by the addition of TBAF (0.505 mL, 0.50 mmol). The reaction mixture was stirred for 20 min. The progress of the reaction was monitored by TLC (2 % MeOH-$CHCl_3$). After completion, the reaction mixture was passed through silica pad; washed initially three times with $CHCl_3$ (3 x 50 mL) then with 50 % mixture of $CHCl_3$-MeOH (2 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The compound **6** was obtained as yellow solid in overall yields of 77 % (195 mg). M.P.: 161.3-163.2 ^{o}C; $[\alpha]_D^{25}$: +17.3 (*c* 0.1 $CHCl_3$), IR (cm^{-1}, film): 2866, 1606,

1091, 840; ^{1}H NMR: δ 7.93(s, 2H, C-9H, C-10H), 7.62 (dd, 8H, *J* = 22 Hz, 2 x CH≡C-*Ph*), 7.23-7.31 (m, 10H, 2 x *Ph*CH_2), 4.76 (s, 4H, 2 x PhC*H*$_2$), 4.53 (s, 4H, C-7H, C-8H), 4.24 (d, 2H, *J* = 4 Hz, C-2H, C-5H), 4.06 (d, 2H, *J* = 4 Hz, C-3H, C-4H), 3.69 (d, 4H, *J* = 4 Hz, C-1H, C-6H), 3.18 (s, 2H, C*H*≡C-); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 146.4 (C), 138.0 (C), 137.1 (C), 133.9 (C), 128.8 (CH), 128.2 (CH), 128.1 (CH), 123.0 (C), 120.9 (CH), 120.5 (CH), 82.6 (CH), 82.1 (CH), 79.4 (CH), 77.0 (CH), 72.3 (CH_2), 71.2 (CH_2), 65.3 (CH_2); HRMS (ESI) *m/z* calcd. for $C_{42}H_{39}N_6O_5$ $[M+H]^+$ 707.2976, found 707.2966.

4.5. Synthesis of macrocyclic compound **7**

A mixture of compound **4** (90 mg, 0.15 mmol), compound **6** (160 mg, 0.14 mmol), $CuSO_4.5H_2O$ (17 mg, 0.05 mmol), sodium ascorbate (23 mg, 0.11 mmol), *S*-phenyl ethyl ammonium acetate (17 mg, 0.14 mmol) was dissolved in *t*-BuOH-water-THF (40 mL, 1:1:2 ratio) and stirred at 30 ^{o}C for 6 h. The progress of the reaction was monitored by TLC. After completion of reaction, the solvent was evaporated under reduced pressure. The compound was purified over silica gel column chromatography using $CHCl_3$-MeOH as elutent. The macrocycle **7** was obtained a yellowish solid in 28 % yield (70 mg). M. P.: 242-244 ^{o}C; UV (λ_{max}, $CHCl_3$): 235 nm; IR (cm^{-1}, film): 2922, 1636, 1500, 1103, 739; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (s, 2H, C-9H, C-10H), δ 7.85 (d, 4H, *J* = 8.8 Hz, =C-*Ph*-N-), 7.76 (s, 2H, C-9'H, C-10'H), 7.65 (d, 4H, *J* = 8.8 Hz, =C-*Ph*-N-), 7.25-7.42 (m, 20H, 4 x *Ph*CH_2), 4.78 (s, 4H, 2 x Ph*CH*$_2$), 4.40-4.66 (m, 12H, C-7H, C-8H, 2 x PhC*H*$_2$, C-2H, C-5H, C-3H, C-4H), 4.22-4.23 (m, 2H, C-2'H, 5'H), 4.00-4.06 (m, 6H, C-1'H, C-6'H, C-3'H, C-4'H), 3.64-3.71 (m, 4H, C-1H, C-6H). HRMS (ESI) *m/z* calcd. for $C_{62}H_{61}N_{12}O_8$ $[M+H]^+$ 1101.4730, found 1101.4730.

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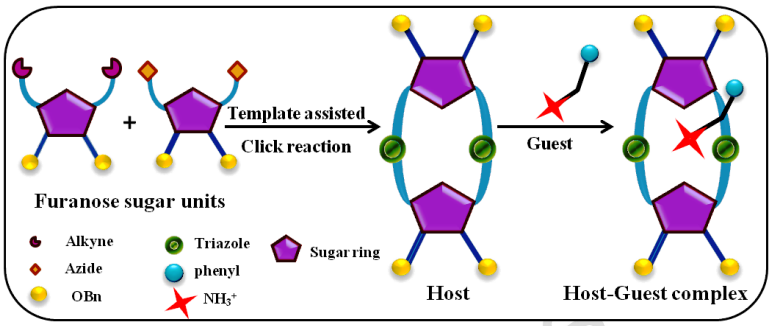


Fig. 1. Template assisted synthesis of chiral sugar-based macrocycles and their interaction with ammonium ion.

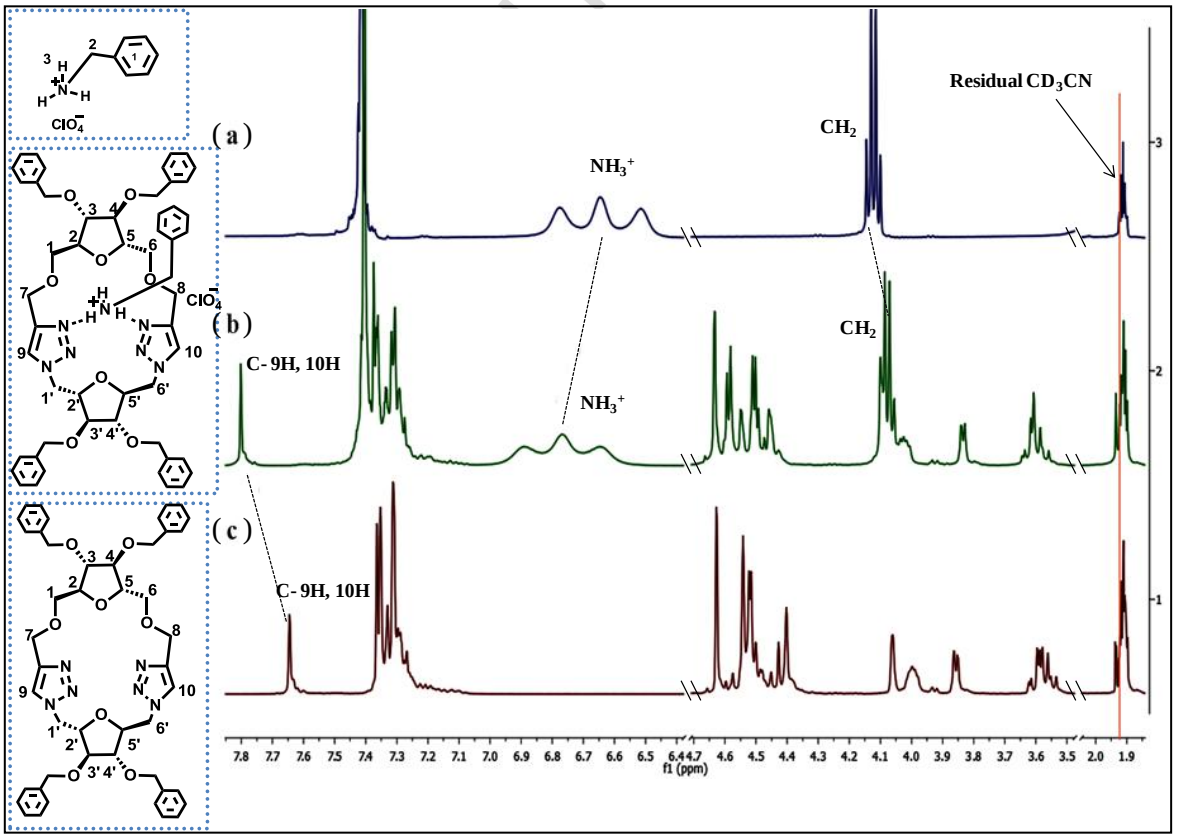


Fig. 2. Stacked partial ^{1}H NMR spectra (400 MHz, CD_3CN) of (a) benzyl ammonium perchlorate salt, (b) mixture of macrocycle 5 and guest salt in 1:1 ratio and (c) macrocycle 5.

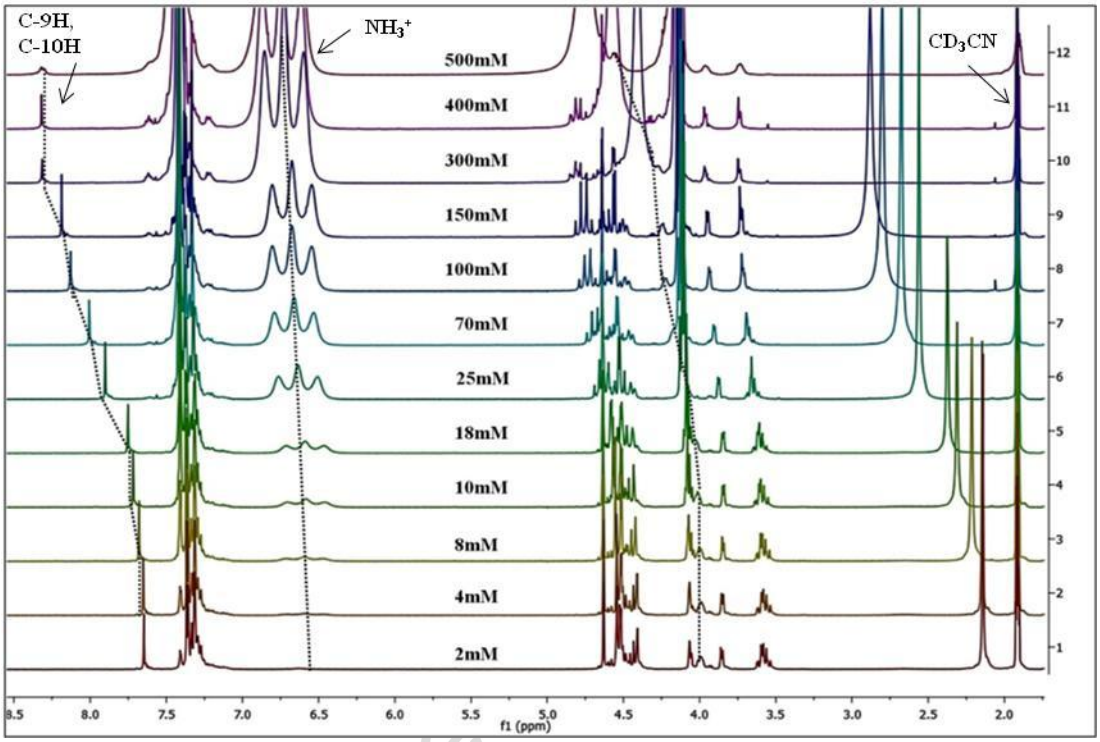


Fig. 3. Stacked partial ^{1}H NMR spectra (400 MHz, CD_3CN) of macrocycle **5** (host, 9.8 mM solution) and benzyl ammonium perchlorate (guest, varying concentration from 2 mM to 500 mM).

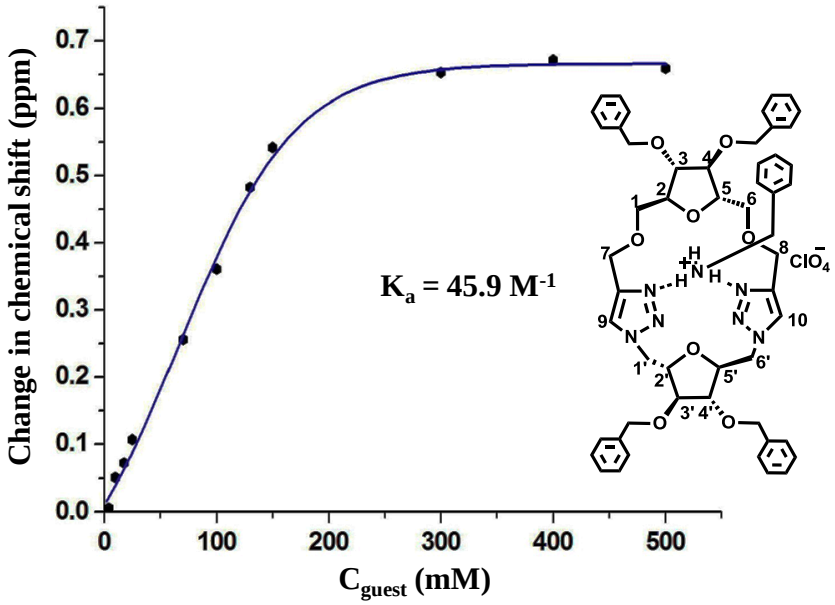


Fig. 4. Graph represents the change in the downfield shift of the triazole ring protons of host **5** with the increase in concentration of guest molecule, *i.e.* benzyl ammonium perchlorate salt. The K_a has been calculated from B-N equation.[26]

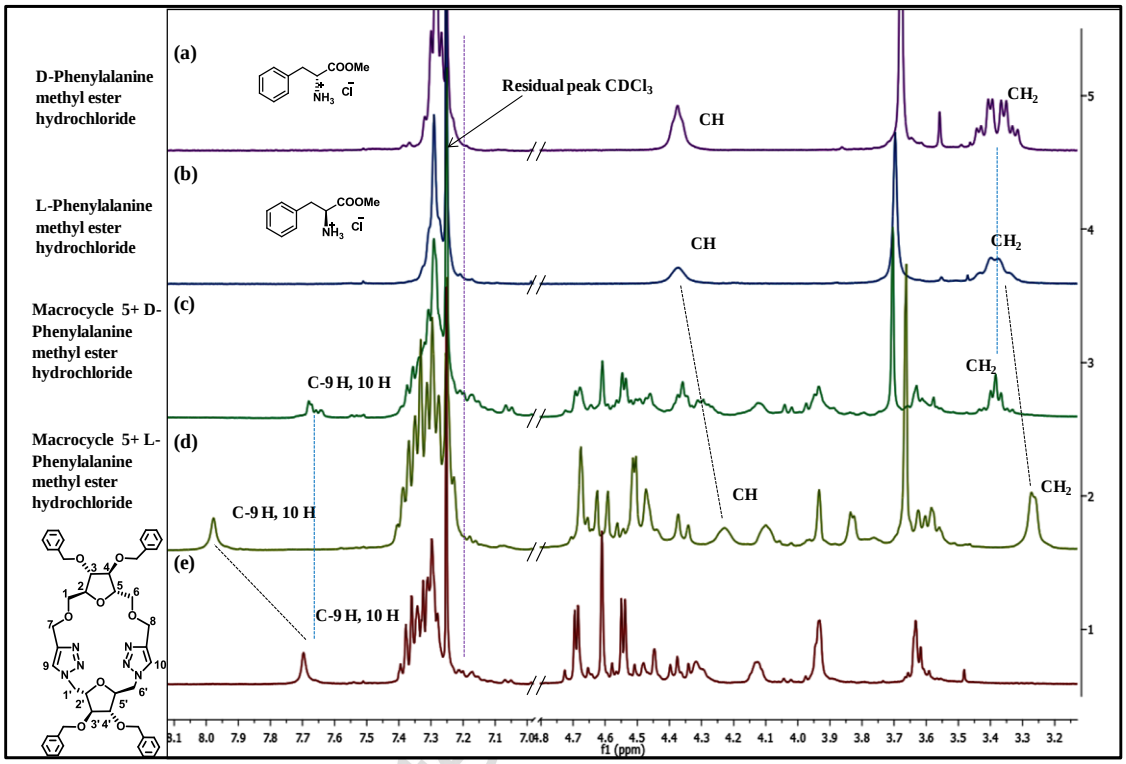


Fig. 5. Stacked partial ^{1}H NMR spectra (400 MHz, $CDCl_3$) (a) D-phenylalanine methyl ester hydrochloride, (b) L-phenylalanine methyl ester hydrochloride, (c) mixture of macrocycle **5** and D-phenylalanine methyl ester salt, (d) mixture of macrocycle **5** and L-phenylalanine methyl ester salt, (e) macrocycle **5**.

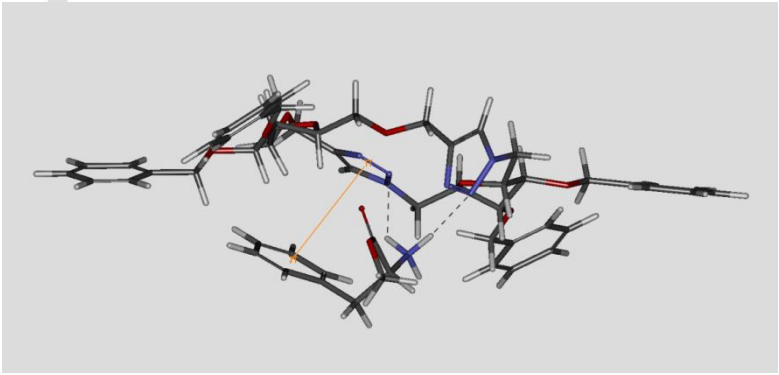


Fig. 6: An energy minimized model presenting geometry optimization of macrocycle **5** and L-phenylalanine methyl ester hydrochloride. The present configuration revealed the interaction of ammonium group of amino acid via hydrogen bonding with the nitrogen atom of triazole ring of host. The π-π interaction between the phenyl group of

amino acid salt with the host triazole ring triggers such hydrogen bonding between host-guest complex. This resulted in the downfield shift of triazole proton of host and upfield shift in the -C*H* proton of the guest molecule in ^{1}H NMR (see Fig. 5).

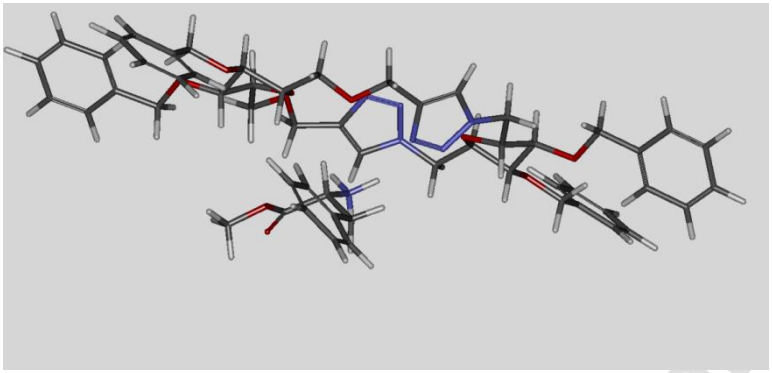
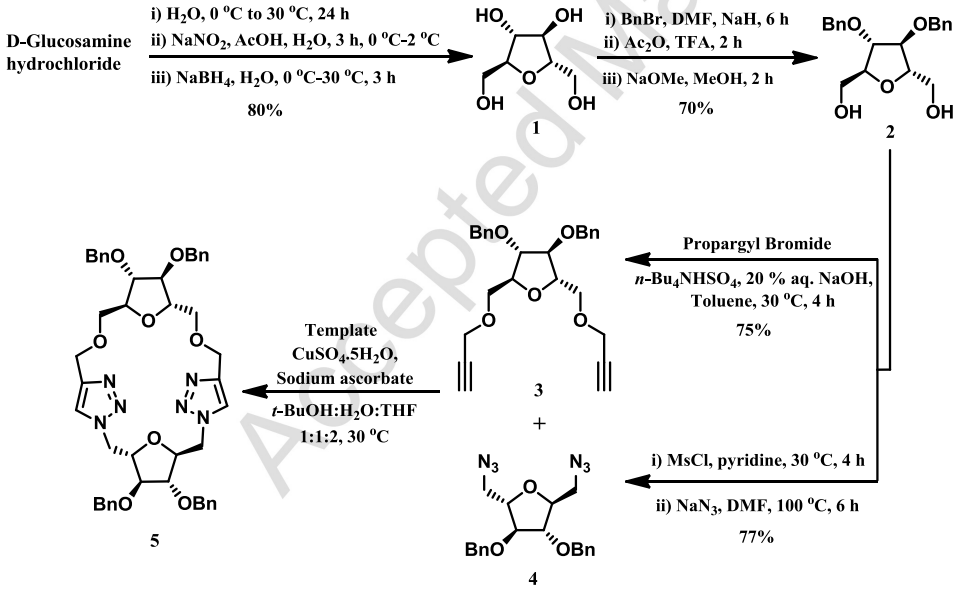


Fig. 7: An energy minimized model presenting geometry optimization of macrocyle **5** and D-phenylalanine methyl ester hydrochloride, it does not reveal interaction between the two moieties.

Scheme 1. Synthesis of macrocycle **5**



Scheme 2. Synthesis of macrocycle **7**

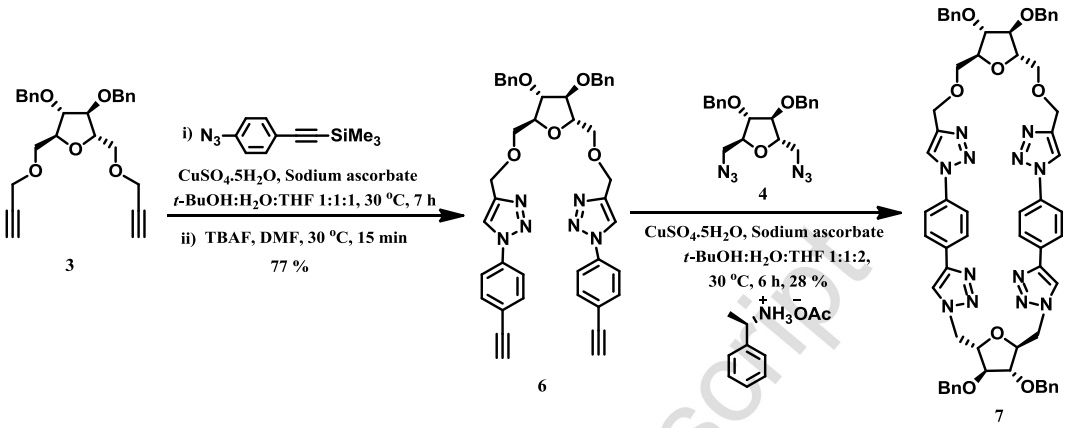
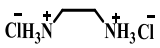
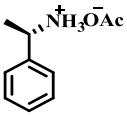
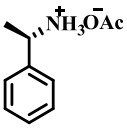
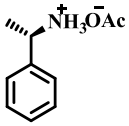


Table 1. Optimization of macrocyclization reaction for the synthesis of macrocycle **5**

Entry	Solvent / 100 mg of equimolar mixture of compds. 3 and 4	Template	Reaction time(h)	Yield (%)
1	1 ml	-	28	6
2	1ml		28	6
3	1ml	 (*S*)	15	18
4	20ml	 (*S*)	6	30

5	20ml	 (*R*)	6	28